PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/70

A1

(11) International Publication Number: WO 98/30223

(43) International Publication Date: 16 July 1998 (16.07.98)

(21) International Application Number: PCT/US98/00634

(22) International Filing Date: 13 January 1998 (13.01.98)

(30) Priority Data:

60/036,094	14 January 1997 (14.01.97)	US
60/028,586	23 April 1997 (23.04.97)	US
60/043,974	23 April 1997 (23.04.97)	US
60/055,487	12 August 1997 (12.08.97)	US

(71) Applicant *(for all designated States except US)*: ICN PHARMACEUTICALS, INC. [US/US]; 3300 Hyland Avenue, Costa Mesa, CA 92626 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: TAM, Robert [US/US]; 1112D Buckingham Drive, Costa Mesa, CA 92626 (US). WANG, Guangyi [US/US]; 17502 Jordan Avenue #9d, Irvine, CA 92715 (US). AVERETT, Devron [US/US]; 26 Trinity, Irvine, CA 92653 (US). RAMASAMY, Kandasamy [US/US]; 5 Rocky Creek Lane, Laguna Hills, CA 92653 (US).

(74) Agent: FISH, Robert, D.; Suite 706, 1440 N. Harbor Boulevard, Fullerton, CA 92835 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
With amended claims.

Date of publication of the amended claims:
1 October 1998 (01.10.98)

(54) Title: CYTOKINE RELATED TREATMENTS OF DISEASE

(57) Abstract

Nucleosides and other compounds to selectively modulate Th1 and Th2 responses relative to each other in the treatment of disease. In one aspect of the invention, administration of a nucleoside or other compound reduces the dosage at which a primary drug is administered. In another aspect of the invention, an abnormality reflected in increased response in one group of cytokines is treated by administering a nucleoside or other compound which increases response in another group of cytokines. In yet another aspect of the invention, a patient is prophylactically treated by administering a nucleoside or other compound which selectively reduces Th1 activity without significantly reducing Th2 activity. In yet another aspect of the invention, a nucleoside or other compound is administered to a patient at a dose which reduces the patient's GTP pool to a degree that selectively reduces one of the Th1 or Th2 response without significantly reducing the other response. Controlled release dosage forms are particularly contemplated to achieve that result.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

AMENDED CLAIMS

[received by the International Bureau on 13 August 1998 (13.08.98);
original claims 1-74 replaced by amended claims 1-74 (7 pages)]

1. A method of reducing an administered dosage of a first drug in the treatment of a disease which is known to produce an abnormality in at least one cytokine in a patient, comprising:

identifying a monotherapeutic dosage of the first drug which is effective to treat the disease;

identifying a second drug as one that exacerbates the abnormality when administered as a monotherapy within a dosage range; and

administering a combination therapy comprising the first drug at less than the monotherapeutic dosage and the second drug outside the dosage range.

2. The method of claim 1 wherein the disease comprises a chronic disease.

3. The method of claim 1 wherein the disease comprises chronic viral disease.

4. The method of claim 1 wherein the disease comprises insulin dependent diabetes.

5. The method of claim 1 wherein the disease comprises allergy.

6. The method of claim 1 wherein the disease comprises atopic dermatitis.

7. The method of claim 1 wherein the disease comprises intracellular protozoan infection.

8. The method of claim 1 wherein the disease comprises hyper IgE syndrome.

9. The method of claim 1 wherein the disease comprises HIV.

10. The method of claim 1 wherein the disease comprises graft versus host disease.

11. The method of claim 1 wherein the disease comprises Systemic Lupus Erythematosus.

12. The method of claim 1 wherein the disease comprises a tumor.

13. The method of any of claims 1-12 wherein the abnormality comprises an abnormal increase in Th1 activity.

14. The method of any of claims 1-12 wherein the abnormality comprises an abnormal decrease in Th1 activity.

15. The method of any of claims 1-12 wherein the abnormality comprises an abnormal increase in Th2 activity.

16. The method of any of claims 1-12 wherein the abnormality comprises an abnormal decrease in Th2 activity.

17. The method of any of claims 1-12 wherein the second drug comprises a pharmaceutically acceptable form of a nucleoside.

18. The method of any of claims 1-12 wherein the second drug comprises a pharmaceutically acceptable form of a D-nucleoside.

19. The method of any of claims 1-12 wherein the second drug comprises a pharmaceutically acceptable form of an L-nucleoside.

20. The method of any of claims 1-12 wherein the second drug comprises a pharmaceutically acceptable form of Ribavirin.

21. The method of any of claims 1-12 wherein the second drug comprises a pharmaceutically acceptable form of an interferon.

22. The method of any of claims 1-12 wherein the second drug comprises a nucleoside according to at least one of Formulas 1, 1A, 1B, 1C, 1D, 1E or 1F.

23. The method of any of claims 1-12 wherein the second drug comprises a nucleoside according to at least one of Formulas 2, 3, 4 or 5.

24. A method of treating a disease in a patient, comprising:

recognizing that the disease is associated with an increase in activity of a first lymphokine phenotype;

recognizing that a particular pharmaceutical is capable of both increasing and decreasing a second lymphokine phenotype depending on the dosage; and

administering the pharmaceutical to treat the disease at least in part by affecting the activity of the second lymphokine phenotype.

25. The method of claim 24 wherein the disease comprises a chronic disease.

26. The method of claim 24 wherein the disease comprises chronic viral disease.

27. The method of claim 24 wherein the disease comprises insulin dependent diabetes mellitus.

28. The method of claim 24 wherein the disease comprises allergy.

29. The method of claim 24 wherein the disease comprises atopic dermatitis.

30. The method of claim 24 wherein the disease comprises intracellular protozoan infection.

31. The method of claim 24 wherein the disease comprises hyper IgE syndrome.

32. The method of claim 24 wherein the disease comprises HIV.

33. The method of claim 24 wherein the disease comprises graft versus host disease.

34. The method of claim 24 wherein the disease comprises Systemic Lupus Erythematosus.

35. The method of claim 24 wherein the disease comprises a tumor.

36. The method of any of claims 24 - 34 wherein the first phenotype is Th2 and the second phenotype is Th1.

37. The method of claim 36 wherein the pharmaceutical comprises a pharmaceutically acceptable form of Ribavirin.

38. The method of claim 36 wherein the pharmaceutical comprises a pharmaceutically acceptable form of an interferon.

39. The method of any of claims 24 - 35 further comprising administering the pharmaceutical in a combination therapy with a therapeutic agent.

40. The method of claim 39 wherein the therapeutic agent is selected from the list consisting of anti-viral agents, anti-fungal agents, bowel agents, anti-tumor agents, dermatologic agents, migraine preparations, steroids, immuno-suppresants and metabolic agents.

41. The method of claim 39 wherein the pharmaceutical comprises a pharmaceutically acceptable form of Ribavirin or an Interferon.

42. The method of claim 39 wherein the first phenotype is Th2 and the second phenotype is Th1.

43. The method of any of claims 24 - 35 wherein the second drug comprises a nucleoside according to at least one of Formulas 1, 1A, 1B, 1C, 1D, 1E or 1F.

44. The method of any of claims 24 - 35 wherein the second drug comprises a nucleoside according to at least one of Formulas 2, 3, 4 or 5.

45. The method of claim 39 wherein the second drug comprises a nucleoside according to at least one of Formulas 1, 1A, 1B, 1C, 1D, 1E or 1F.

46. The method of claim 39 wherein the second drug comprises a nucleoside according to at least one of Formulas 2, 3, 4 or 5.

47. A method of prophylactically treating a patient comprising:

providing a pharmaceutical which suppresses Th1 activity in the patient when administered above a given dosage level; and

administering the pharmaceutical to the patient below the given dosage level.

48. The method of claim 47 wherein the prophylaxis comprises preparing the patient for an organ transplant.

49. The method of claim 47 wherein the prophylaxis comprises preparing the patient for a tissue transplant.

50. The method of claim 47 wherein the prophylaxis comprises preparing the patient for expected contact with allergens.

51. The method of any of claims 47 - 49 further comprises providing the pharmaceutical at a dosage which induces Th2 activity.

52. The method of any of claims 47 - 49 wherein the pharmaceutical comprises a nucleoside according to at least one of Formulas 1, 1A, 1B, 1C, 1D, 1E or 1F.

53. The method of any of claims 47 - 49 wherein the pharmaceutical comprises a nucleoside according to at least one of Formulas 2, 3, 4 or 5.

54. A method of treating a disease having an elevated or suppressed Th1 or Th1 response, comprising:

identifying a compound and a dosage range for the compound as having efficacy in reducing the patient's GTP pool and thereby selectively reducing one of the Th1 or Th2 response without significantly reducing the other response; and

administering the nucleoside to the patient within the dosage range.

55. The method of claim 54 wherein the disease comprises a chronic disease.

56. The method of claim 54 wherein the disease comprises chronic viral disease.

57. The method of claim 54 wherein the disease comprises insulin dependent diabetes mellitus.

58. The method of claim 54 wherein the disease comprises allergy.

59. The method of claim 54 wherein the disease comprises atopic dermatitis.

60. The method of claim 54 wherein the disease comprises intracellular protozoan infection.

61. The method of claim 54 wherein the disease comprises hyper IgE syndrome.

62. The method of claim 54 wherein the disease comprises HIV.

63. The method of claim 54 wherein the disease comprises graft versus host disease.

64. The method of claim 54 wherein the disease comprises Systemic Lupus Erythematosus.

65. The method of claim 54 wherein the disease comprises a tumor.

66. The method of any of claims 54 - 65 wherein the compound comprises a nucleoside according to at least one of Formulas 1, 1A, 1B, 1C, 1D, 1E or 1F.

67. The method of any of claims 54 - 65 wherein the compound comprises a nucleoside according to at least one of Formulas 2, 3, 4 or 5.

68. A controlled release preparation for oral administration including a compound effective to selectively modulate Th1 and Th2 responses with respect to each other within a dosage range, the controlled release aspect of the preparation assisting in maintaining a serum level below that which would suppress both Th1 and Th2 responses.

69. The controlled release compound of claim 68 wherein the compound comprises a nucleoside according to at least one of Formulas 1, 1A, 1B, 1C, 1D, 1E or 1F.

70. The controlled release preparation of claim 68 wherein the compound comprises a nucleoside according to at least one of Formulas 2, 3, 4 or 5.

71. The controlled release preparation of claim 68 wherein the compound comprises Ribavirin.

72. The controlled release preparation of claim 68 wherein the compound comprises an interferon.

73. The controlled release preparation according to any of claims 68 - 73 wherein the patient maintains a serum level of between about 2 μM and about 5 μM of the compound.

74. The controlled release preparation according to any of claims 68 - 73 wherein the preparation has an *in vitro* dissolution rate when measured by the USP Paddle Method at 100 rpm at 900 ml aqueous buffer (pH between 1.6 and 7.2) between about 15% and 40% by weight of the compound after 1 hour, between about 30% and about 50% by weight of the compound after 2 hours, about 50% and 70% by weight of the compound after 4 hours, between about 60% and about 80% by weight of the compound after 6 hours.